Immunopathogenesis of Psoriasis

ARTIGO DE REVISÃO BIBLIOGRÁFICA

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Estudante: Anabela Ribeiro Faria De Carvalho

Aluna do 6º ano profissionalizante do Mestrado Integrado em Medicina

Nº 201008377

Orientador: Prof. Doutor Tiago Torres

Grau de Especialista em Dermatologia

Hospital de Santo António, Centro Hospital do Porto.

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Abstract

Psoriasis is a chronic systemic inflammatory skin disease of a complex etiology, involving genetic, immunological and environmental factors, in response to numerous triggers. The goal of this study is to summarize current available data on the importance of T-cells in conjunction with the innate immune system, involved in the immunopathogenesis of psoriasis.

The genetics of psoriasis is complex and multifactorial. Genetic predisposition of the disease appears to play an important role in the susceptibility to develop psoriasis, with several different susceptibility loci (PSORS1–10) being identified, specifically HLA-Cw6 within PSORS1 being identified as the major genetic determinant for psoriasis.

Initially, psoriasis was considered solely to be due to the dysfunction of limiting keratinocyte proliferation. Infiltration of immune cells was noticed, but not considered to be key in the pathogenesis, and rather just a consequence of the hyper-proliferating keratinocytes. Involvement of the immune system in psoriasis is now widely accepted. Psoriatic skin lesions originate as a result of dysregulated interactions and amplification of innate and adaptive components of the immune system with resident cutaneous cell types. The major pathogenic pathway in psoriasis occurs when mature dermal dendritic cells (DCs) and inflammatory myeloid DCs produce cytokines such as interleukin (IL)-23 and IL-12 to activate IL-17 producing T-cells, T-helper (Th) 1 cells, and Th22 cells. These cells are responsible for producing an abundance of psoriatic cytokines including IL-17, interferon-gamma, tumor necrosis factor-alpha, and IL-22. In response, epidermal keratinocytes upregulate messenger ribonucleic acid for a range of inflammatory products and produce chemokines and antimicrobial peptides, leading to an amplified and sustained psoriatic inflammation response. IL-23/Th17 is now recognized as the major axis of the psoriatic immune pathway.

The understanding of the immunopathogenesis of psoriasis has resulted in several highly specific therapies. These therapies target specific components of the immune system, proving the importance of further research and the need of a comprehensive understanding of the immunopathogenesis of psoriasis, in order to significantly attenuate the patient's signs and symptoms, and ultimately improve their quality of life.

Keywords: Immunopathogenesis; Psoriasis; Keratinocytes; T-cells; Dendritic cells; Interleukin 23; Interleukin 17.

Resumo

A psoríase é uma doença dermatológica crónica, sistémica e inflamatória, de uma etiologia complexa, que envolve fatores genéticos, imunológicos e ambientais, em reposta a numerosos “triggers”. Esta revisão bibliográfica tem como objetivo resumir os diversos estudos disponíveis sobre a importância das células T, em conjunto com o sistema imune na imunopatogénese da psoríase.

A genética da psoríase é complexa e multifactorial. A predisposição genética para a doença parece desempenhar um papel importante na suscetibilidade ao seu desenvolvimento, identificando-se diversos loci de suscetibilidade diferentes (PSORS1-10), com particular relevância do HLA-Cw6 no PSORS1, identificado como o principal determinante genético da psoríase.

Inicialmente, a psoríase foi considerada apenas como sendo devido à disfunção em limitar a proliferação dos queratinócitos. A presença de células do sistema imune foi observada, mas não considerada um mecanismo chave na patogénese, e sim apenas uma consequência desta hiperproliferação. O envolvimento do sistema imune na patogénese da psoríase é atualmente amplamente aceite. As lesões cutâneas da psoríase originam devido a interações desreguladas e amplificadas das células do sistema inato e adaptativo com as células cutâneas. A via patogénica principal na psoríase ocorre quando as células dendríticas (DCs) maduras da derme e as DCs mieloides inflamatórias produzem citocinas como a interleucina (IL-) 23 e IL-12, ativando as células T produtoras de IL-17, as células T-helper (Th) 1 e as células Th22. Estas células são responsáveis pela produção de um número abundante de citocinas psoriátricas, incluindo a IL-17, o interferão-gama, fator de necrose tumoral-alfa e a IL-22. Em resposta a esta citoquinas, os queratinócitos da epiderme sobre-regulam a expressão de mensageiros do ácido ribonucleico para vários produtos inflamatórios e produzem quimiocinas e peptídeos antimicrobianos, levando à amplificação e sustentação da resposta inflamatória. A via IL-23/Th17 é atualmente reconhecida como a principal via na resposta imune da psoríase.

A compreensão da imunopatogénese da psoríase resultou no desenvolvimento de vários fármacos específicos para o tratamento da doença. Este fármacos têm como alvo componentes específicos do sistema imune, comprovando a importância de futuros estudos nesta área e a necessidade de uma compreensão abrangente da imunopatogénese da psoríase, a fim de atenuar significativamente os sinais e sintomas dos doentes com psoríase e melhorar a sua qualidade de vida.

Palavras chave: Imunopatogénese; Psoríase; Queratinócitos; Células T; Células Dendríticas; Interleucina 23; Interleucina 17.

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Abbreviation List

α – Alpha

AMPs – Antimicrobial Peptides

β – beta

DCs – Dendritic Cells

DNA - Deoxyribonucleic Acid

EDC – Epidermal Differentiation Complex

$Foxp3^{+}$ – Forkhead/Winged Helix Transcription Factor 3

γ – Gamma

GWAS – Genome-Wide Scan

ICAM – Intercellular Adhesion Molecule

IFN – Interferon

IL – Interleukin

ILC3 – Innate Lymphoid Cells

iNK – Invariant Natural Killer

iNOS – Inducible Nitric Oxide Synthase

Jak2 – Janus Kinase-2

LCs – Langerhans Cells

LL37 – Cathelicidin

mDCs – Myeloid Dendritic Cells

MHC – Major Histocompatibility Complex

mRNAs – Messenger Ribonucleic Acids

NF-κB – Nuclear Transcription Factor-κB

NO - Nitric Oxide

NK – Natural Killer

PASI – Psoriasis Activity and Severity Index

pDCs – Plasmacytoid Dendritic Cells

R – Receptor

RNA – Ribonucleic Acid

STAT – Signal Transducer and Activator of Transcription

Tc – T Cytotoxic ells

Th – T-helper

TLR – Toll Like Receptor

TNF – Tumor Necrosis Factor

Treg – Regulatory T-cell

Tyk2 – Tyrosine Kinase-2

VEGF – Vascular Endothelial Growth Factor

I. Introduction

Psoriasis is a chronic systemic inflammatory skin disease that affects about 2-3% of the worldwide population [1].

The exact mechanisms of psoriasis immunopathogenesis is not completely recognized [2]. There is considerable evidence indicating that psoriasis pathogenesis is a complex interaction between genetic, immunological, and environmental components [3]. Several environmental factors have been shown to trigger the first episode of psoriasis in individuals genetically predisposed [4]. These triggers include physical trauma (sunburn and surgery), psychological stress, infections (bacterial pharyngitis and human immunodeficiency virus type 1) and drugs (β-blockers, angiotensin-converting enzyme inhibitors, antimalarials cloroquine, tetracyclines, nonsteroidal anti-inflammatory drugs and lithium) [4-6]. Psoriasis is also associated with multiple co-morbidities including arthritis, inflammatory bowel disease, cardiovascular disease, obesity, hypertension, diabetes mellitus, and depression [7].

Plaque-type psoriasis is the most common form, affecting 80 to 90% of patients [8]. It typically presents as erythematous plaques covered with a silvery white scale, that can easily be removed, revealing focal bleeding points (the Auspitz sign) [9]. Lesions often begin as small papules that expand and coalesce to form extensive psoriatic plaques. These lesions are typically distributed symmetrically on the scalp, elbows, knees, and lumbosacral area [5]. Histologically, psoriasis lesions are characterized by acanthosis, loss of the granular layer, parakeratosis, hyperkeratosis, angiogenesis and a dense infiltration by immune cells, namely T-cells, dendritic cells (DCs) and macrophages [10, 11]. These immune effectors produce pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), IL-17, IL-22, IL-23 and IL-1 beta (β). Neutrophils collect in the epidermis and form collections called Munro's microabscesses. Plaques are highly vascular and new vessel formation is mediated by angiogenic factors such as vascular endothelial growth factor (VEGF) [7].

Genetic and immunology research have converged to shape the current pathogenic model for psoriasis, highlighting the key roles of the innate and adaptive immune pathways [7]. Keratinocytes are key participants in innate immunity recruiting T-cells to the skin, and T-cells are important in sustaining disease activity. Inflammatory myeloid DCs release IL-23 and IL-12 to activate IL-17 producing T-cells (T cytotoxic cell 17 and Th17), Th1 cells, and Th22 cells to produce abundant psoriatic cytokines IL-17, IFN-γ, TNF-α, and IL-22. These cytokines mediate effects on keratinocytes to amplify psoriatic inflammation [12-14]. Several studies suggest that psoriasis is a Th17 cell-mediated disease controlled by IL-23. TNF-α also stimulates CD11+ inflammatory DCs to produce IL-23 and IL-20 and seems to be a critical cytokine for many of the pathogenetic features of psoriasis [3].

A search in the PubMed database (up until April 2017) for articles with the specific keywords: Immunopathogenesis, Psoriasis, Keratinocytes, T-cells, Dendritic cells, Interleukin 23, and Interleukin 17, present in the title, abstract, or body was performed. The reference lists of those articles were examined to retrieve other studies that were considered relevant and contributive to the scientific purpose of the present review but had not been retrieved by the database search. Therefore, this article summarizes current knowledge regarding the immunopathogenesis of psoriasis.

II. Psoriasis

The pathogenesis of psoriasis involves dynamic interactions between multiple cell types and numerous cytokines in response to triggers in genetically predisposed individuals, culminating in the disruption of skin immune homeostasis [7].

Initially, psoriasis was considered to solely be due to a dysfunction of limiting keratinocyte proliferation. Infiltration of immune cells was noticed, but not considered to be relevant, and rather just a consequence of the hyper-proliferating keratinocytes [1]. The evidence that the immune system (T-lymphocytes and dendritic cells) played a more integral role in psoriasis has come with clinical and translational research involving human subjects, as administration of immune suppressive agents, such as Cyclosporine, Denileukin Diftitox, and Alefacept, proved successful in improving disease [1, 12].

Psoriasis pathogenesis includes hyper-proliferation and aberrant differentiation of keratinocytes, inflammation and dermal angiogenesis [9]. Histological features in psoriasis include proliferation and aberrant differentiation of epidermal keratinocytes, hyperkeratosis, infiltration of immune cells and subsequent typical thickening of the erythematous skin. The epidermis is greatly thickened (acanthosis), with elongation of the rete ridges that protrude down into the thickened papillary dermis. This epidermal thickening is due to a dramatic increase in the proliferation of psoriatic keratinocytes at the base of the epidermis. This leads to reduced maturation of the cells as they journey outward and retention of keratinocyte nuclei, which can be seen in the scaly layer (the stratum corneum) as parakeratosis. Collections of neutrophils can also be seen in the epidermis and stratum corneum. These histological features give rise to the characteristic clinical observation of a silvery scale shown by almost all psoriasis lesions. In the dermis, there is elongation and dilation of the dermal blood vessels that protrude up between the rete ridges, giving rise to the red color of psoriasis lesions. These dermal blood vessels and surrounding upper dermal spaces are filled with leukocytes, including DCs, neutrophils, macrophages, and mast cells, as well as T-cells [3, 10].

Although the exact mechanisms for the induction of psoriasis are not yet fully elucidated, Gilliet and Lande have suggested a model of psoriasis initiation involving toll like receptors (TLRs), antimicrobial peptide LL37 (cathelicidin) released by keratinocytes, and plasmacytoid dendritic cells (pDCs) [15]. When triggering factors cause skin injury, keratinocytes produce LL37 in response, which then mediates the breakdown of tolerance to self-nucleic acids. LL37 binds with pathogen-derived deoxyribonucleic acid (DNA) or self-DNA that has been released by stressed or dying cells and form DNA/LL37 complexes that bind to intracellular toll like receptor (TLR) 9 on pDCs. This promotes type I IFN-α and -β activation and release, which along with TNF-α, IL-6 and IL-1β, activates local myeloid DCs,

thus promoting T-cell mediated inflammation. LL37 may also bind to self-ribonucleic acid (RNA) and directly activate pDCs through TLR7 and myeloid DCs via TLR8 [7, 12, 16].

Myeloid DCs migrate into draining lymph nodes and release cytokines including TNF-α, IL-23 and IL-12 that activate allogeneic T-cells. Once activated, T-cells enter the circulation and move towards inflamed skin through interactions with adhesion molecules (P-selectin and E-selectin) on the endothelial cells of blood vessels. The effector molecules secreted by T-cells then activate keratinocytes, resulting in the release of cytokines and chemokines that continue to recruit and activate inflammatory cells. IFN-γ, IL-17 and IL-22 are secreted by Th1, Th17 and Th22 cells, respectively, which contribute to the amplification of cutaneous inflammation [7]. IFN-γ promotes hyper-proliferation of keratinocytes by inhibiting apoptosis and increases intercellular adhesion molecule (ICAM) 1 expression in the endothelial cells, facilitating lymphocyte circulation. IL-17 interacts with IFN-γ, increasing the synthesis of pro-inflammatory cytokines by keratinocytes (IL-6 and IL-8), which increases the chemoattraction of T-cells into the skin, helping to maintain the psoriasis plaque [4].

The roles of different T-cell subsets in psoriasis, including Th1 (IFN-γ), Th17 (IL-17), and Th22 (IL-22), have been dissected through the testing of a range of cytokine antagonists. From this network of chemical mediators IL-23 and IL-17 look like the most interesting molecules to be investigated. The first specific indication that the immune system could be playing a more integral role came with the clinical trial targeting T-cells with a fusion protein also called Denileukin Diftitox, that causes apoptosis in activated T-cells expressing functional IL-2 receptors. In mice, a topical biologic response modifier Imiquimod (TLR7 agonist) induces psoriasiform skin inflammation mediated by the IL-23/Th17 axis and activated DCs. Therefore, TLRs may trigger signal-transduction pathways that turn on expression of genes with important functions in psoriasis. The immune circuit described previously is amplified by the reaction of keratinocytes and myeloid DCs. In response to cytokines from each of the T-cell subsets, keratinocytes upregulate messenger RNAs for a range of inflammatory products, which feedback on immune cells in the skin so that chronic T-cell activation persists [4, 12, 16].

Recently IL-36 has driven the attention of several investigators with its role in triggering psoriasis and is a good candidate as a target molecule for new therapies in the future. IL-36 is a key molecule for innate immunity dysfunction in psoriasis. Furthermore it is able to cross-talk with keratinocytes and dendritic cells producing TNF-α and has regulatory functions on IL-23/IL-17/IL-22, the main pathways investigated in psoriasis in the last years [4].

III. Genetic Studies

Several studies have demonstrated that genetic predisposition has an important role in the susceptibility to develop psoriasis. The likelihood of developing psoriasis is raised when first-grade relatives suffer from the disease. The risk is about 20% if one parent has psoriasis, and is about 75% if both parents are affected [11]. These studies also show that the concordance rate for dizygotic twins is only 22% compared with a high rate of 72% for monozygotic twins [4].

One of the earliest candidate genes for predisposition to psoriasis was the HLA class I allele, specifically HLA-Cw6 [6]. People with HLA-Cw6, for example, have a 10-fold higher risk of disease [11]. HLA class I and II antigens such as HLA-B13, -B17, -B39, -B57, -Cw7, -DR4 and -DR7 also have been shown to be positively associated with the pathogenesis of psoriasis [4]. Early onset psoriasis (before 40 years) has been reported to have a stronger genetic basis, because a greater proportion of patients had a family history of psoriasis, more severe disease, and stronger HLA associations [5].

By using genome-wide scans (GWAS), investigators have mapped (with varying degrees of confidence) at least several different susceptibility loci, designated PSORS1–PSORS10 [6]. Major susceptibility loci for psoriasis have been established at chromosome 6p21.3 (PSOR1), whereas other associations have been reported on chromosomes 17q (PSORS2), 4q (PSORS3), 1cenq21 (PSORS4), 3q21 (PSORS5), 19p (PSORS6), 1p (PSORS7), and 4q31 (PSOR9) (Table 1) [5, 17]. The major genetic determinant for psoriasis is within the PSORS1 region of the MHC, as reported by several independent groups, accounting for 30–50% genetic susceptibility. The likely causal allele within PSORS1 is HLA-Cw6, which encodes a class I major histocompatibility complex (MHC) molecule that is expressed by antigen presenting cells and mediates T cell activation. The second most well characterized disease-susceptibility locus (PSORS2) resides within 17q24–q25. Linkage of psoriasis to this locus has been identified by independent family sets [6, 7].

Gene/locus	Chromosomal location	Candidate gene(s)	Reference(s)
PSORS2	17q	*RUNX1*, *RAPTOR*, *SLC9A3R1*, *NAT9*, *TBCD*	268–270
PSORS3	4p	*IRF-2*	271, 272
PSORS4	4q	*Loricrin*, *filaggrin*, S100 genes, *LCE*	69, 71, 72
PSORS5	3q	*SLC12A8*, *cystatin A*, *ZNF148*	273, 274
PSORS6	19p	*JUNB*	275, 276
PSORS7	1p	*IL23R*, *PTPN22*	54–56, 277
PSORS8	16q	*CXCL1*, *CX3R1*, *CARD15*	269
PSORS9	4q	*IL15*	278
PSORS10	18p	—	279

Table 1: Psoriasis susceptibility loci (PSORS) 2–10 [17].

Several psoriasis-associated genes belonging to the IL-23/Th17 axis, the nuclear transcription factor-κB (NF-κB) signaling pathway, and the epidermal differentiation complex (EDC) have been identified, which suggests that these pathways are critically involved in psoriasis pathogenesis [17].

Also genes expressed within keratinocytes that promote innate responses to viral nucleic acids and are upregulated in psoriatic skin lesions have been found by GWAS to confer disease susceptibility. The RIG-I and MDA5 innate antiviral receptors, encoded by the psoriasis-associated genes DDX58 and IFIH1, respectively, bind to viral double-stranded RNA and promote the release of pro-inflammatory cytokines that have been implicated in psoriatic lesion initiation such as type I IFN, IL-1, IL-6, and IL-29. Dysregulated antiviral immunity may contribute to the development of psoriasis by promoting the over-production of pro-inflammatory cytokines by keratinocytes [7].

IV. Innate Immunity

1. Dendritic Cells

DCs are professional antigen presenting cells that activate T-cells and are an important source of pro-inflammatory cytokines and chemokines in psoriasis. In the skin, the main DC populations include epidermal DCs (Langerhans cells) and dermal DCs (myeloid and plasmacytoid).

Myeloid DCs (mDCs) express a distinct cell surface marker, CD11c, which is considered to be important in the early stages of disease. The blood DC antigens identify different subsets of myeloid DCs, such as BDCA-1+ “resident” DCs and BDCA-1- “inflammatory” DCs. Both these DCs can stimulate T-cells robustly in an allogeneic mixed lymphocyte reaction and similarly induce allogeneic T-cells to produce IFN-γ and IL-17 [7, 12]. During psoriatic inflammation there is a 30-fold increase in CD11c+ mDCs in the dermis of psoriatic skin lesions compared with uninvolved psoriatic or normal skin (BDCA-1- “inflammatory” DCs, not the BDCA-1+ “resident” DCs). A large proportion of these DCs express TNF and the enzyme-inducible nitric oxide synthase (iNOS). TNF-α induces expression of ICAM-1 in keratinocytes, stimulates keratinocytes and dermal fibroblasts to produce IL-8, as well as pro-inflammatory cytokines (IL-6 and IL-1) that stimulate Th17. The important role of TNF-α will be explained in more detail in this article. iNOS is not usually found in normal resting cells but is induced in response to inflammatory stimuli. It is the enzyme responsible for the generation of nitric oxide (NO). In the skin, NO plays many roles, including vasodilation, inflammation, and an antimicrobial effect. Along with TNF-α and

iNOS, “inflammatory” DCs produce other pathogenic cytokines, such as IL- 20, which enhances keratinocyte activation and proliferation, and IL-23, which aids in differentiation, proliferation, and survival of Th17 cells (Figure 1) [10, 16].

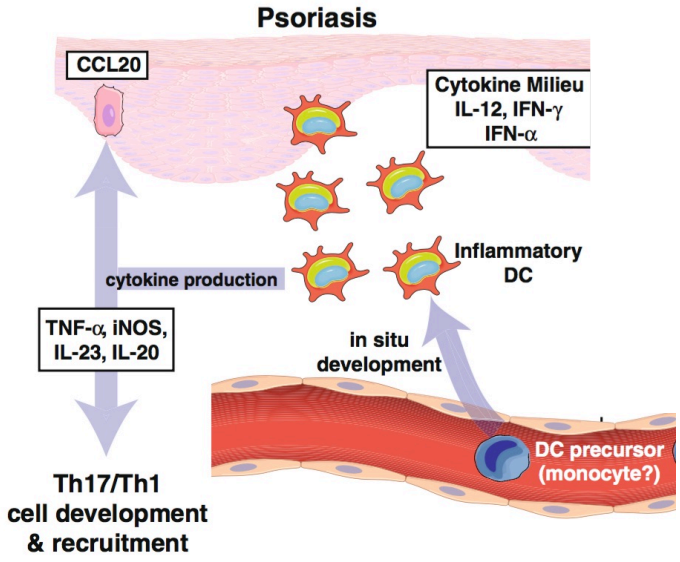

Figure 1: The development and function of myeloid inflammatory DCs in psoriasis. As a result of cytokine production in the cutaneous microenvironment, DC precursors differentiate into inflammatory DCs in situ. Depending on the environmental cues, inflammatory DCs produce a distinct set of cytokines. Psoriatic DCs produce TNF-α, NO, IL-20, and IL-23 and are involved in the development and maintenance of a Th1/Th17 polarized response [10].

Plasmacytoid DCs are a rich source of type I IFN, an early signature cytokine in psoriasis. Type I IFNs comprise IFN-α and IFN-β, amongst others. In the case of psoriasis, tolerance to self-DNA can be broken, so self-DNA forms aggregates with LL37. LL37/DNA complexes prevent DNA degradation by nucleases and allow for endocytosis by pDCs to initiate disease. Sustained interactions of self-DNA with intracellular TLR9 induce production of large amounts of IFN-α. Type I IFN promotes myeloid DC phenotypic maturation and activation, thus facilitating T-cell priming. Type I IFN signaling modulates the production of IFN-γ and IL-17 and has been implicated in the differentiation and activation of T-cells, in particular Th1 and T17 cells [7, 10, 18].

Langerhans cells (LCs) are a type of immature antigen-presenting cells that reside in the epidermis [12]. The main role of LCs is to take up and process antigens or cytokines and migrate to local skin-draining lymph nodes where they present to antigen-specific T-cells [16]. However, the role of LCs in psoriasis immunopathogenesis is still unclear [17]. Recently, attention has focused on the potential importance of LCs in uninvolved skin sites of patients with psoriasis and it has been demonstrated that LC migration is impaired in early onset psoriasis (before 40 years of age) [12]. Treatment with TNF-α inhibitors (Adalimumab,

Etanercept) and anti-p40 antibody (Ustekinumab) significantly restored epidermal LC migration in uninvolved skin. Therefore, the loss of LC motility may have an impact on the ability of these cells to sense the local antigenic microenvironment and regulate cutaneous immune responses [12]. LCs in human skin preferentially activate Th2 and Th22 cells, based on ex-vivo functional analyses [16]. In a series of elegant experiments co-culturing epidermal CD1a+ LCs and T-cells from healthy skin of the same donor, Seneschal et al. showed that LCs could induce a regulatory T-cell (Treg) phenotype (CD3+ CD4+ CD25hi Foxp3+) [19].

2. Keratinocytes

Keratinocytes are believed to be crucial in both the early stages of disease pathogenesis and later amplification of chronic inflammatory circuits. They form the body's first line of defense against exogenous physical, chemical and microbial insults. Genetic studies indicate a role for skin barrier dysfunction in psoriasis since deletion of LCE3B and LCE3C genes, encoding stratum corneum proteins involved in terminal differentiation of the epidermis, was found to be associated with psoriasis [7].

Keratinocytes respond to different danger signals, and orchestrate innate and adaptive immune responses, releasing antimicrobial peptides (AMPs) such as LL37, β-defensins, S100 proteins, peptide-glycan recognition proteins, calcium-dependent lectins (C-type lectins), and iron-metabolizing proteins such as lipocalin 2. These molecules have direct antimicrobial activity and also help to modulate immune cells by promoting the upregulation of pro-inflammatory cytokines such as IL-6 and IL-10 and chemokines such as IL-8 (CXCL8) and CXCL10. Keratinocytes may release these neutrophil chemoattractants in response to T-cell-derived inflammatory cytokines to drive neutrophil migration into the epidermis (Figure 2) [7, 12, 17, 20].

The most likely initiator of the keratinocytes activation cycle is IL-1. Both the α and β isoforms of IL-1 are stored unprocessed in the cytoplasm of the cells as pro-IL-1α and pro-IL-1β. When pattern-recognition receptors and Nod-like receptors recognize their ligands, caspase-1 is activated within the keratinocytes [17]. Activation of caspase-1 possibly cleaves pro-IL-1α, pro-IL-1β, and pro-IL-18, which help to initiate the cutaneous inflammatory response to injury. IL-1β effects the production of TNF-α by local keratinocytes and upregulates leucocyte chemotactic proteins (selectins), which promote the skin infiltration and activation of T-cells. IL-18 and IL-1β are further involved in the differentiation of Th1 cells and Th17 cells, respectively [14]. This sets up positive feedback loops as activated Th1 and Th17 cells release IFN-γ, IL-22 and IL-17, which drives keratinocyte proliferation and activation, hence contributing to the formation of a cutaneous plaque [7]. IL-17 also induces CCL20 expression from keratinocytes, which plays a central chemotactic role for inflammatory T-cells and DCs, and may provide an autocrine loop to increase the influx of

Th17 cells themselves. IL-22 modulates a set of genes involved in keratinocyte mobility and terminal differentiation. IL-22 is responsible for disrupting normal keratinocyte differentiation in psoriasis, resulting in epidermal hyperplasia and hypogranulosis. Both IL-17 and IL-22 can induce keratinocyte expression of the antimicrobial S100A7 (psoriasin), which in turn mediates further leucocyte chemotaxis. IFN-γ induces keratinocyte expression of CXCL9, CXCL10 and CXCL11 that contribute to the trafficking of CD8+ T-cells, into the psoriatic lesion [7, 17].

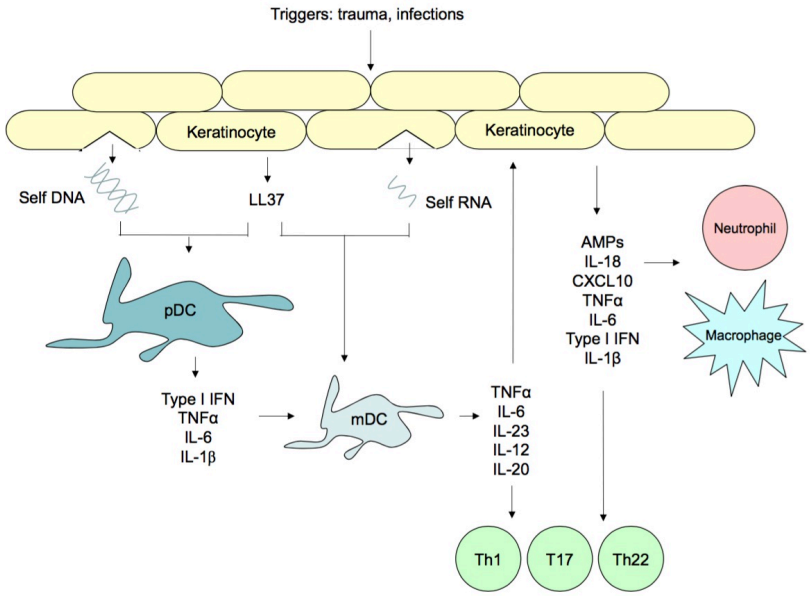

Figure 2: Schema for the initiation of a psoriatic skin lesion. Triggers such as trauma and infections lead to the release of self-DNA and self-RNA, which form complexes with LL37 and activate pDCs and mDCs, respectively. pDCs secrete type I IFN and other cytokines including TNF-α, IL-6 and IL-1β, which promote the activation of mDCs. These antigen presenting cells release pro-inflammatory cytokines that drive T-cell mediated inflammation and keratinocyte activation and proliferation. This promotes the recruitment and activation of further inflammatory cells such as neutrophils and macrophages, contributing to the formation of an inflamed cutaneous plaque. AMPs antimicrobial peptides [7].

Keratinocytes also produce cytokines and angiogenic factors, such as VEGF during inflammatory states, which induces angiogenesis by promoting the migration, survival and proliferation of endothelial cells, resulting in the formation of an erythematous and vascular plaque [7, 17].

3. Macrophages

The role of macrophages in psoriasis is not yet fully characterized, but they probably contribute to the pathogenic inflammation in psoriasis by releasing key inflammatory

cytokines. Macrophages are present in psoriatic lesions and, via production of TNF, are thought to take part in the development of skin inflammation in psoriasis [7, 12, 17].

Macrophages show a three-fold increase in cell numbers in psoriatic lesional skin, with evidence of normalization after successful treatment. Cutaneous macrophages can be identified by their expression of CD163 (a myeloid cell hemoglobin/haptoglobin scavenger receptor), and activated macrophages produce high levels of TNF-α and are likely to regulate angiogenesis via the release of VEGF [7, 16].

Although, they have long been recognized as antigen-presenting cells, capable of activating memory T-cells during stimulation of the adaptive arm of the immune response, contrary to dendritic cells, they are unable to polarize allogeneic T-cells to produce IL-17 in psoriasis [12, 21].

4. Neutrophils

Neutrophils are important in the early stages of psoriasis as they are involved in the recruitment and activation of T-cells and the proliferation and differentiation of keratinocytes [7]. Neutrophils are reportedly attracted to the skin by a number of chemotactic factors, including IL8/CXCL8, CXCL1, CXCL2, and IL-18. Keratinocytes produce chemokines in response to IL-17, and the receptors for these chemokines are on skin-infiltrating neutrophils. Neutrophils within the epidermis and stratum corneum (Kogoj and Munro's microabscesses, respectively) produce reactive oxygen intermediates and proteolytic enzymes thought to promote local tissue destruction, unmask hidden antigens, or affect growth and differentiation of keratinocytes [20]. Elastase is a protease that is released by neutrophils in response to TNF-α or IL-8. It has several downstream effects, including the induction of keratinocyte proliferation and cleavage of cytokines into their active forms [7].

5. Mast Cells

Mast cells are said to be involved in the pathogenesis of psoriasis [22]. Activated keratinocytes attract immune effector cells including mast cells, which further contribute to the pro-inflammatory environment producing cytokines and chemokines [9]. Mast cells secrete large amounts of TNF-α, IFN-γ, IL-8, and other mediators such as VEGF, to recruit neutrophils and lymphocytes during innate and T-cell mediated inflammation [5, 22].

Mast cells, particularly a subset containing tryptase and chymase, are enriched in the papillary dermis of psoriasis lesions [23]. Notably, mast cells staining positive for IL-17 were identified at higher densities than IL-17+ T-cells in psoriatic lesions [24]. In several human autoimmune and neurodegenerative diseases, including psoriasis, it has been shown that mast cells also produce several members of the IL-17 family (IL-17E which can influence Th2 type responses and IL-17A) [8, 9, 25, 26]. Mast cells frequently degranulate in early

eruptive and recurring psoriasis lesions and have been described as “ghost cells”. Increased mast cells and neutrophils release IL-17 into the skin though process of extracellular trap formation, conventional degranulation, and through the mechanistic stimulus of IL-23 and IL-1β [23].

6. Natural Killer Cells

Natural killer (NK) T-cells are a heterogenous subset of T-cells that share features of both T-cells and NK cells [9]. Classically, NK T-cells are divided into three subsets: type I, or invariant NK (iNK) T, type II NK T and NK T-like cells [27]. In psoriatic lesions, the amount of NK T-cells is also increased in comparison with normal skin [11]. Although the exact role of NK and NK T-cells in psoriasis have not been thoroughly explored, it has been suggested that these innate immune cells may play a role in psoriasis by releasing several inflammatory cytokines, such as IFN-γ, TNF-α, and IL-22 [1, 12]. However, the function of NK and NK T-cells has not yet been fully understood, and further studies are required to evaluate their contribution to psoriasis [12, 16].

V. Adaptive Immunity

A pivotal study demonstrated that inhibition of lymphocyte, but not keratinocyte, proliferation improved symptoms in patients with psoriasis, suggesting that psoriasis is a complex immune-mediated inflammatory disease driven primarily by T-cells [5, 24]. This conclusion concurred with immunohistochemical staining of psoriatic lesions showing CD3+ T-cells surrounding capillaries and CD4+ and CD8+ T-cells predominating in the dermis and epidermis, respectively [24]. This is supported by the effectiveness of several T-cell directed therapies in causing disease resolution. The first successful drug was DAB389IL-2, an IL-2 fusion protein that causes apoptosis of activated T-cells expressing functional IL-2 receptors. The observed beneficial effects of other agents such as Abatacept (CTLA-4-Ig), which blocks T-cell co-stimulation, Alefacept an LFA-3-Ig fusion protein that inhibits effector memory T-cell activation, and Cyclosporine A (a substance that diminishes T-cell proliferation and cytokine production), further re-enforced the important pathogenic activity of this cell type in psoriasis [2, 5, 7, 24].

The importance of abnormal T-cell activation in the pathogenesis of psoriasis has been highlighted by several genetic studies that demonstrate a strong disease association between certain major histocompatibility complex class I alleles (such as HLA-Cw6, HLA-B17, and HLA-Bw57) and psoriasis [2, 7].

T-cells can be subdivided into two classes: CD8+ cytotoxic T-cells and CD4+ helper T-cells, both which are found to be increased in psoriasis [1]. Several CD4+ T-cells discretely produce IFN-γ, IL-17, and IL-22, with initial labeling of these cells as Th1, Th17, and Th22, respectively. There are also CD8+ T-cell populations, in the presence of IL-7 and IL-15 that make the same range of cytokines, so these have been termed T cytotoxic cells (Tc) 1, 17, and 22, respectively [2, 12].

The presentation of cutaneous antigens by DCs in the skin stimulates the proliferation of antigen-recognizing T-cells and memory effector cells (Figure 3) [17, 22]. After antigen stimulation, T-cells enter the circulatory system and interact with adhesion molecules (P-selectin and E-selectin) in endothelial cells of blood vessels [5, 11]. This interaction with adhesion molecules allows the migration and accumulation of T-cells, as well as macrophages, DCs, NK cells, and neutrophils through the blood vessel wall into the skin and around dermal blood vessels [5]. It has been postulated that an initial dermal helper T-cell (CD4+) infiltrate and trigger sequences of events that is obligatory for CD8+ T-cells to present their effector function [2]. The lymphocytic infiltrate and resident T-cells play important roles in preceding and stimulating hyper-proliferation and disrupt the differentiation process by interacting with keratinocytes. Expression of activation and memory markers on CD4+ and CD8+ lymphocytes point to the importance of these cells in the pathophysiology of psoriasis [2, 22].

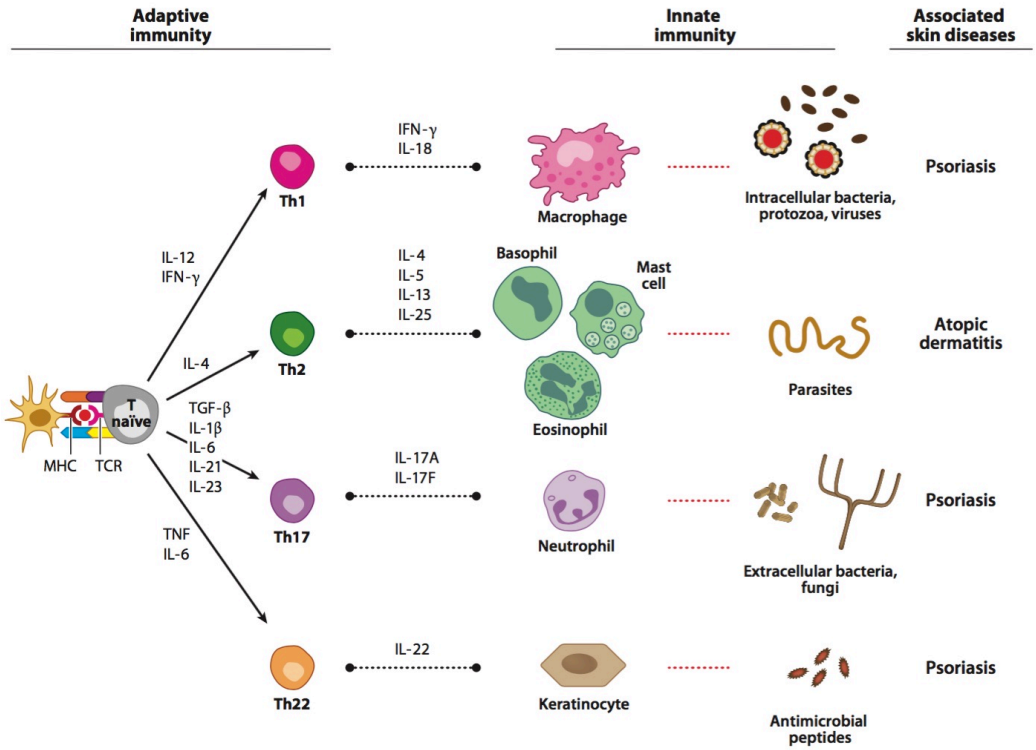

Figure 3: Dendritic cells provide antigen presentation, co-stimulatory signals and cytokines to induce differentiation of naive T-cells into effector subsets. Th1 cells differentiate in the presence of IL-12 and

IFN-γ and produce IFN-γ and IL-18. These cytokines, in turn, facilitate macrophage-mediated immunity against intracellular bacteria, protozoa, and viruses. Th2 cells develop in the presence of IL-4 and release IL-4, IL-5, IL-13, and IL-25. Th2 cells are important for cellular immunity against parasites and helminths mediated by basophils, eosinophils, and mast cells, as well as components of humoral immunity. Th17 cells require a combination of transforming growth factor (TGF)-β and pro-inflammatory cytokines (IL-1β, IL-6, IL-21, and IL-23) to differentiate. They produce IL-17A, IL-17F, and IL-22 and are important in neutrophil-mediated protection against extracellular bacteria and fungi as well as in keratinocyte production of AMPs. Recently identified Th22 cells differentiate from naive T-cells in the presence of TNF and IL-6 and produce IL-22. IL-22 acts on epithelial cells, for instance, keratinocytes, which proliferate and increase their production of AMPs [17].

1. Interferon-gamma/T helper 1

Naive CD4+ T-cells differentiate into Th1 cells in the presence of IL-12, and produce mainly IFN-γ, IL-2, and lymphotoxin. Cytokines produced by these cells activate macrophages and participate in the generation of T cytotoxic cells, leading to a cell-mediated anti-viral immune response. Th2 cells develop in the presence of IL-4, and produce IL-4, IL-5, and IL-13, that mediate humoral immunity [2, 7].

Evidence suggests that a shift in the balance between the Th1 and Th2 immune responses may play a role in promoting autoimmune reactions and immune dysfunction [2]. Psoriasis has traditionally been classified as a Th1 disease because of a predominance of Th1 pathway cytokines, such as TNF-α, IFN-γ, IL-2, and IL-12 in peripheral blood and psoriatic plaques of patients [4, 5, 9]. The data also suggest that IFN-γ in the serum of psoriatic patients was much higher than that of the control group, and correlated with the disease severity expressed as psoriasis activity and severity index (PASI) score, whereas Th2 cytokine (IL-4 and IL-10) levels were found to be lower. Since then, it has been widely recognized that the interaction of T-cells and DCs creates a 'type 1' inflammatory environment by secreting large amounts of Th1 type cytokines, leading to the development of psoriasis [9]. The exact mechanism responsible for Th1/Th2 polarization is not clear. There is increasing evidence to indicate that two transcription factors, T-bet and GATA-3, are the determining factors for Th1 and Th2 cell differentiation, respectively [2].

Dendritic cells can instruct T-cells during priming to adopt a Th1 fate through secretion of the cytokine IL-12. IL-12 is composed of two subunits, p35 and p40. It was found that p40 expression is increased in psoriasis [1]. When the Th1 differentiation pathway is activated, IFN-γ and TNF-α are produced [24].

Activated Th1 cells are defined by their expression of IFN-γ and IL-18, in addition to TNF and IL-1 [17]. IFN-γ is a type II IFN, also secreted by DCs and NK cells. It is postulated that IFN-γ is more relevant in the early stages of disease, accelerating the migration of immune cells into the skin and activating antigen presenting cells (monocytes, macrophages,

DCs, and endothelial cell) [5, 7]. It also stimulates chemokines (CXCL10 and CXCL11), adhesion molecule release from keratinocytes, epidermal cell proliferation and inhibits the apoptosis of keratinocytes, causing the hyper-proliferation of keratinocytes observed in psoriatic plaques [22]. IL-12 secreted by DCs, together with IL-2 from T-cells, regulate the transcription of IFN-γ and TNF-α [5]. However, the dominant role of IFN-γ in psoriasis is now less clear after the discovery of IL-17 [28]. Most likely the IL-12/IFN-γ axis does not participate directly in maintaining chronic skin disease in psoriasis, because selective blockade of IL-23 leads to full resolution of psoriasis based on clinical, histologic, and molecular disease markers. In the clinical trial of IL-23 specific monoclonal antibody, high levels of IL-12 and IFN-γ mRNA were maintained, whereas IL-17 levels were dramatically reduced in patients with psoriasis. Direct blockade of IFN-γ with a neutralizing antibody in patients with psoriasis was shown to have little or no therapeutic benefit, suggesting this cytokine does not directly drive the psoriasis phenotype in chronic lesions [12].

2. Tumor Necrosis Factor

TNF-α is an important cytokine of the Th1 pathway [5]. TNF-α is produced by several different cells types in the context of cutaneous inflammation, including macrophages, keratinocytes, Th1 cells, Th17 cells, Th22 cells and BDCA-1 inflammatory DCs [7]. TNF-α regulates the ability of DCs to activate T-cells and stimulates the proliferation of cytokines, and adhesion molecules. It induces the expression of C-reactive protein, a key protein in the acute phase response, and IL-6. IL-6 mediates T-cell activation, stimulates keratinocyte hyper-proliferation and mediates the acute-phase response [5, 7, 22]. TNF-α also increases expression of CCL20, a chemokine that recruits mDCs and Th17 cells, and IL-8, a cytokine that provides a strong chemotactic signal for the recruitment of neutrophils. TNF-α promotes the infiltration of inflammatory cells such as T-cells and monocytes into the skin, through the upregulation of ICAM-1 [7]. TNF-α is an activator of IL-23 synthesis in DCs and enhances the effects of other cytokines relevant to psoriasis pathogenesis such as IL-17 [7, 12]. Therefore, the clinical benefit seen with TNF-α inhibitor biologics as therapy (Infliximab, Adalimumab and Etanercept) is linked to suppression of the IL-23/Th17 axis [3, 12, 24]. Although TNF-α blockade is very effective therapeutically, the diverse actions of the cytokine have resulted in numerous drug-associated side effects [7].

3. Interleukin 23/T helper 17

Evidence is accumulating to suggest that IL-23 and its resulting Th17 pathway play a more important role in psoriasis than IL-12 [29]. IL-23 and IL-12 share the common p40 subunit, however IL-23 is produced by the combination of p40 with the p19 subunit, whereas

IL-12 is composed of p40 and p35 subunits [10, 18]. In psoriasis lesions, IL-23 is produced by BDCA-1 “inflammatory” DCs, BDCA-1+ “resident” DCs and macrophages, that mediate the terminal differentiation and activation of Th17 cells (including induction of IL-17A and IFN-γ), activation of keratinocytes and upregulation of TNF-α expression in macrophages, which in turn, drives and sustains the psoriatic disease process [4, 7, 12, 18].

The IL-23 receptor (R) is a heterodimeric receptor, composed of IL-12RB1 and IL-23R. These receptor components lack intrinsic signaling activity, and signal through the interactions with downstream molecules [1]. IL-12B1 requires tyrosine kinase-2 (Tyk2) for signaling, whereas IL-23R requires janus kinase-2 (Jak2) [1, 4]. When Jak2 and Tyk2 are activated, this leads to the phosphorylation of the receptor complex and consequently to the activation of the transcription factors signal transducer and activator of transcription (STAT) 3 and 4 which up regulate IFN-γ and allow Th17 differentiation, with its downstream secretion of IL-17A and other Th17 products [4].

In the case of psoriasis, the hypothesis that IL-12 was a driver of disease was based, in part, on detection of the p40 subunit in psoriatic lesions, which could have represented IL-23 [24]. Results of numerous studies have indicated that levels of p19 and p40 mRNA, but not p35 mRNA, are substantially increased in psoriatic lesional skin compared with psoriatic non-lesional skin [18]. GWAS studies that link single nucleotide polymorphisms in/near IL-23R, IL-23A, IL-12B, TYK2 and STAT3 with psoriasis susceptibility have highlighted IL-23 as a critical cytokine in disease pathogenesis [1, 7].

The importance of IL-23 in psoriasis pathogenesis has been further confirmed by the clinical improvements in patients through targeting this cytokine in the treatment of psoriasis [1, 18]. Monoclonal antibody treatment targeting especially the IL-23 specific p19 subunit have demonstrated outstanding clinical efficacy [1]. The most advanced of these agents are Tildrakizumab (humanized Ig-G1k monoclonal anti-IL-23p19 antibody that does not bind to IL-12 or p40) and Guselkumab (human IgG1 monoclonal anti-IL-23 antibody), both of which have shown promising results in phase 2 trials. BI 655066 is a human IgG1 monoclonal anti-IL-23A antibody that is ongoing phase 2 studies in patients with moderate-to-severe chronic plaque psoriasis [18].

Th 17 cells are CD4+ effector Th cells that are distinct from the classic Th1 and Th2 lineages. Th17 cells differentiate from naive T-cells after stimulation by TGF-β, IL-6, IL-21, and IL-1β [30]. Th17 cells also activated by the combination of IL-23 and IL-1α or IL-1β, to produce multiple inflammatory cytokines [2, 4]. Th17 cells generate various cytokines such as IL-17A, IL-17F, IL-21, IL-22, IL-26, TNF-α and the chemokine CCL20, that play essential roles in a variety of chronic inflammatory diseases, including psoriasis [4, 9, 31].

Evidence is now emerging that IL-17 is a key cytokine in the immunopathogenesis of psoriasis at the keratinocyte level [18]. The Th1 hypothesis of psoriasis pathogenesis was

revised after recognition that Th17 cells are a key T-cell population in lesional skin [24]. IL-17 consists of a family of six members (IL-17A-F), with the role of IL-17A in psoriasis being the most extensively researched [7, 18]. Levels of IL-17A, IL-17F and IL-17C are significantly increased in psoriatic patients compared to healthy subjects [2, 4, 30]. IL-17C has recently been demonstrated to act on keratinocytes to induce pro-inflammatory cytokines, chemokines and AMPs, and this activity requires both IL-17 receptor (IL-17R) E and A [32]. Gene set enrichment analysis of the psoriasis transcriptome also reveals enrichment for IL-17A genes [2, 12]. More recently, IL-17A or the IL-17R A subunit blocking agents have been shown to have rapid and high efficacy in clinical trials, showing a reverse in clinical, histologic, and molecular features of psoriasis in approximately 80% of patients with psoriasis given higher levels of the antagonists [7, 12]. Secukinumab, a monoclonal antibody that targets IL-17A, has been approved for the treatment of moderate-to-severe psoriasis [18]. A monoclonal antibody that inhibits IL-17A (Ixelkizumab) and monoclonal antibody that blocks the IL-17R (Broadalumab) are being researched for the treatment of psoriasis [26]. RG7624, an antibody that targets both IL-17A and IL-17F, is also being investigated for the treatment of psoriasis but no clinical trial results have been reported for this agent [25].

IL-17A acts on a variety of cell types including endothelial cells, fibroblasts, chondrocytes, synovial cells, monocytes, macrophages, dendritic cells, neutrophils, lymphocytes and epithelial cells including keratinocytes [2, 4, 30]. Keratinocytes are the predominant cells that express IL-17R in psoriasis [7]. There are a number of genes associated with psoriasis that may function downstream of the IL-17R signaling, such as TRAF3IP2 that codes for the Act-1 protein (also known as TRAF3-interacting protein 2), an intracellular protein that directly binds the IL-17R complex [33]. Act-1 can initiate two different signal transduction pathways in response to IL-17R activation: NF-κB signaling and stabilization of mRNAs induced by TNF [30]. NF-kB signaling events can be initiated through interactions with TRAF6, which induces expression of neutrophils, T-cells, and DC chemokines that lead to the migration of neutrophils, memory T-cells, and DCs to psoriatic lesions [4, 7, 18]. In the TRAF6-independent pathway, Act-1 can bind to TRAF5 and sequester the RNA binding factor SF2, leading to stabilization of inflammatory mRNAs [34]. Keratinocytes in turn are stimulated by IL-17A to produce AMPs, pro-inflammatory cytokines such as IL-19 (driving epidermal hyperplasia), IL-1, IL-6, and IL-23 and chemokines such as IL-8 (recruitment of neutrophils, T-cells and NK cells) [7, 24]. Neutrophils are attracted to the epidermis of psoriatic lesions by chemokines released from IL-17A-stimulated keratinocytes (CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, and CXCL8), affecting the growth and differentiation of keratinocytes [4, 18]. IL-17A also increases production of the chemokine CCL20 and ICAM-1, which facilitate cutaneous recruitment of DCs and T-cells [7]. IL-17A increases the expression of antimicrobial peptides, including members of the β-defensin and

S100A families, thus stimulating the innate immune system. IL-17A has other effects on keratinocytes that can contribute to epidermal hyper-proliferation and skin barrier disruption: it increases expression of keratin, reduces expression of filaggrin, and alters expression of multiple genes involved in cell adhesion [24]. Moreover, DCs and keratinocytes in the skin lesions of psoriasis produce increased amounts of IL-23, a cytokine that promotes the development and proliferation of Th17 cells [2]. This process is illustrated in Figure 4 [30].

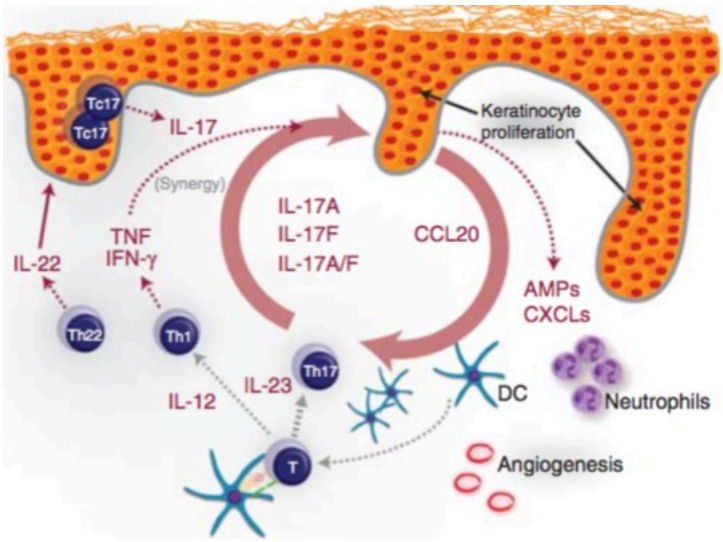

Figure 4: A model for the central role of IL-17 in psoriasis pathogenesis. This model includes core inflammatory elements that establish a self-reinforcing cycle, including Th17 skewing of naive T cells in the presence of IL-23 leading to the local production of IL-17 ligands. Keratinocytes in turn are stimulated by these IL-17 ligands, leading to an aberrant differentiation program and elevated production of pro-inflammatory factors including antimicrobial peptides and chemokines (including CCL20, which attracts both Th17 cells and DCs). These keratinocyte-derived factors in turn stimulate further recruitment of inflammatory cells, including IL-17–producing cells, and establish a self-sustaining inflammatory feedback loop. CXCLs, CXC ligands, Tc and TNF [30].

IL-17A and other Th17 effector cytokines lead to further keratinocyte activation and inflammatory mediator production, thereby creating positive feedback loops such that epidermal hyperplasia and the cutaneous inflammatory response are sustained and amplified in the psoriatic lesion [7, 24]. IL-17 has recently been shown to act in synergy with TNF-α to induce pro-inflammatory cytokine production by keratinocytes and is therefore considered the most important pathogenic stimulant of keratinocytes in psoriasis [7, 12].

4. Interleukin 22/T helper 22

IL-22 is a member of the IL-10 family of cytokines (along with IL-10, IL-19, IL-20, IL-24, and IL-26) and has been found to be upregulated in the skin and sera of patients with psoriasis [7, 35]. The production of IL-22 by Th22 cells and Th17 cells is induced by IL-23,

and has profound effects on epidermal keratinocytes, inducing hyperplasia, migration, and curtailing the normal differentiation pathway as well as the induction of a broad range of cytokines, chemokines, and acute-phase proteins from various inflammatory cells [5, 7, 35]. IL-22 has long been suspected of having a crucial role in the development of psoriasis skin lesions. This cytokine, along with the other IL-20 subfamily members, is upregulated in lesional psoriasis epidermis as well as in the blood of psoriasis patients and is restored to normal levels during effective treatment [35, 36].

IL- 22 has been shown to act in synergy with IL-17A to induce AMP production by keratinocytes [9]. Blockade of IL-22 in vivo or genetic deletion caused reduced IL-23-induced epidermal hyperplasia, and IL-23-mediated epidermal hyperplasia in a murine model of psoriasiform skin inflammation was found to be dependent on IL-22. These data highlight potential crosstalk between the IL-23/Th17 pathway and IL-22/Th22 [7]. IL-22 has somewhat defied the paradigm of classification into the strict Th1, Th2, and Th17 categories, with IL-22 secretion reported from Th1, Th17, and Tc22 cells as well as the more recently appreciated Th22 cells that produce IL-22 in the absence of IFN-γ, IL-4, or IL-17 [35]. In addition, several phenotypes of innate immune cells have been reported to produce IL-22, including NK cells, γδ T-cells, lymphoid tissue inducer cells, and type 3 innate lymphoid cells (ILC3). As such Th17, Th22, Tc22, ILC3, and NK cells have all been reported to be increased in number in psoriasis plaques [37]. The profound effects of IL-22 on skin are further heightened by powerful synergies with IL-17 and TNF, greatly amplifying its effects as well as those of IL-17 and TNF on the cytokine network in psoriasis [35]. However, in contrast to the IL-23/Th17 pathway, there is a lack of genetic data in support of a role for IL-22 in disease pathogenesis [7].

5. γδ T-cells

Unlike dendritic epidermal γδ T-cells and conventional αβ T-cells, dermal γδ T-cells constitutively express IL-23 receptor, CCR6 and the transcriptional factor RORγt. More importantly, these cells are demonstrated to be the major IL-17 producer in the skin upon IL-23 stimulation [9, 16]. In spite of their essential role in the normal host defense, γδ T-cells may also be involved in the pathogenesis of various skin diseases such as psoriasis [2]. Various authors have identified high numbers of γδ T-cells producing IL-17 in psoriatic skin lesions and suggesting a reciprocal relationship between IL-23 and γδ T-cells in the pathogenesis of psoriasis [38]. γδ T-cells in peripheral blood have been characterized as Vγ9Vδ2 (skin homing T-cell), CLA+ and CCR6+, and were able to produce IL-17A and activate keratinocytes via TNF and IFN-γ [12]. Psoriatic skin lesions have greatly increased numbers of γδ T-cells compared with healthy controls, and an IL-17 producing γδ T-cell population has been identified in the dermis [39]. Consequently, γδ T-cells may act in an

amplification loop for IL-17 synthesis and provide an alternative mechanism that may mediate autoimmune inflammation [2, 9].

6. Regulatory T-cells

Tregs are a subset of T lymphocytes that suppress not only autoimmune responses but also other aberrant or excessive immune responses to non-self-antigens [9]. Tregs use diverse pathways to maintain immune tolerance, including release of inhibitory cytokines, induction of apoptosis, and inhibition of IL-2 secretion. Some naturally occurring circulating Tregs can be identified as CD41, $CD25^{high}$ (IL-2R), forkhead/winged helix transcription factor 3 ($Foxp3^{+}$), and CD127 ($IL\text{-}7R^{-}$) [12, 16].

When effector T-cells are not being sustained by Tregs, unstrained effector T-cell effects lead to autoimmunity [40]. Some studies have shown Tregs to be dysfunctional in psoriasis, with decreased suppressive capacity, suggesting that psoriasis may result from the inability to suppress auto-inflammation [12]. In fact, regulatory $CD4^{+}$ T-cells from peripheral blood from patients with psoriasis have been shown to be deficient in their suppressor activity. Moreover, in psoriatic plaques, psoriatic regulatory T-cell population demonstrated decreased suppression of effector T-cells [11]. However, further studies are needed to evaluate Tregs contribution in psoriasis, as function of skin-derived Tregs has not yet been well examined [12].

VI. Conclusion

Molecular and cellular understanding of psoriasis pathogenesis has evolved considerably in the last decade. The precise knowledge of the immunological mechanisms of psoriasis, characterizing the role of each cytokine involved in psoriasis inflammation, made it possible to recognize it as a systemic disease. Psoriasis was initially thought to be a skin disease driven by keratinocyte hyper-proliferation, but the role of the immune system and T-cells in psoriasis pathogenesis has been largely recognized.

The presence of the IL-12 cytokine in psoriatic lesions led researches to postulate that psoriasis was mediated by Th1 cells. Instead of the traditional view regarding psoriasis as a Th1 type disease, it is clearer that collectively, Th1, Th17, Treg, Th22, IFN-γ and TNF-α can cause keratinocyte proliferation and cytokine, chemokine, and antimicrobial peptide production. This becomes a self-amplifying loop, where these products act back on the DCs, T-cells, and neutrophils to perpetuate the cutaneous inflammatory process. Additionally, IL-17A, the principal effector cytokine of Th17 cells, stimulates keratinocytes to produce chemokines, cytokines, and other pro-inflammatory mediators thereby enabling IL-17A to bridge the innate and adaptive immune systems to sustain chronic inflammation.

Clinical and translational research in human subjects has enabled a better understanding of the immunology of psoriasis, and subsequently the development of novel immune-targeted therapeutics. Selected target therapy starting from anti TNF-α, together with the understanding of cytokine networks in psoriasis drove to new specific target biologic therapies such as anti-IL-23/IL-17. IL-23/Th17 is now recognized as the major axis of the psoriatic immune pathway, and antagonists to IL-23 or IL-17 result in the ability to control most of the signs and symptoms of clinical disease of patients with psoriasis.

Thus, psoriasis is considered to be an organ-specific T-cell-driven inflammatory disease and T-cells play a dominant pathogenic role in the initiation and maintenance of psoriasis. The understanding of the immunopathogenesis of psoriasis is not only important because it allows us to identify the key components responsible for inducing and sustaining this disease, but it widely enhances our ability to use this information in order to create new and more effective treatment options that can significantly attenuate the patients signs and symptoms, ultimately improving patients quality of life.

VII. References

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